PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case B-22	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07777	International filing date *(day/month/year)* 17.07.2003	Priority date *(day/month/year)* 18.07.2002
International Patent Classification (IPC) or both national classification and IPC C07C69/92		
Applicant J. URIACH Y COMPANIA et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.01.2004	28.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Kardinal, S Telephone No. +31 70 340-3483

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07777

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-36 as originally filed

Claims, Numbers

1-22 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-21 (partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-21 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,16,18-22
	No:	Claims	14,15,17
Inventive step (IS)	Yes:	Claims	1-13,19-22
	No:	Claims	14-18
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Remark : The scope of claims 1-21, in as far as the expression 'prodrug' is concerned, is so unclear (Article 6 PCT) that a meaningful search has been impossible with regard to this expression. Accordingly the following reasoned statement covers only those parts of claims 1-21 relating to the compounds described in claims 1-21 and the salts and solvates thereof.

1. Reference is made to the following documents:

   D1: I. R. HARDCASTLE ET AL.: TETRAHEDRON LETTERS., vol. 42, no. 7, 2001, pages 1363-1365, XP004316654
   D2: US-A-5 374 772 (CARSON MATHEW ET AL) 20 December 1994
   D3: US-A-4 871 769 (DIAMANTINI GIUSEPPE ET AL) 3 October 1989
   D4: I. R. HARDCASTLE ET AL.: BIOCHEMICAL PHARMACOLOGY, vol. 57, 1999, pages 801-809, XP002259805
   D5: MARYADELE J. O'NEIL (ET AL.) (EDS.).: "THE MERCK INDEX" 2001, MERCK & CO., INC , NEW YORK , XP002259806

2. Novelty

   2.1 Document D1 discloses (cf. page 1365, table 1, product 1g) a compound falling within the scope of formula I of claims 14 and 17 with R1=H, R2=H, R3=3-fluoropropyl and R4=R5=R6=F in an assay for testing the activity versus farnesyl transesterase. With respect to the technical details of the assay, D1 refers to (cf. page 1365, reference [15]) the document D4. Document D4, being part of the disclosure of D1, discloses (cf. page 805, left-hand column) that a solution of the inhibitor compound in DMSO is used in the assays.

   The solvent DMSO has to be considered a pharmaceutical acceptable excipient and shows furthermore itself a range of pharmaceutical activities (cf. D5).

   Hence, the D1 discloses a pharmaceutical composition falling within the scope of claims 14 and 15 and a product comprising a compound of formula I and an additional drug (DMSO) falling within the scope of claim 17.

   The subject-matter of claims 14, 15 and 17 is therefore not novel (Article 33(2) PCT). Dependent claims 16 and 18 can only meet the PCT requirements when

related to independent claims complying with Article 33 (1) PCT.

2.2 The document D2 discloses (cf. columns 1-2) ethers and esters of 2,4-dihydroxy benzoic acid for use in the treatment of psoriasis.

2.3 The document D3 discloses 2-trichloroacetoxy-tetrachlorobenzoic acid for use in the treatment of benign neoformations.

2.4 The compounds according to claim 1 differ from these known compounds structurally. The compound of D1 is disclaimed in present claim 1.

The subject-matter of independent claim 1 and dependent claims 2-11 is therefore novel (Article 33(2) PCT).

2.5 The document D1 discloses a compound falling within the scope of formula I of claims 12, 13, 19, 21 and 22 as being inactive in an enzyme activity test. No therapeutical application is disclosed. The process of preparation disclosed in D1 uses a bicyclic ester acetal (cf. page 1364, scheme 2) and does not fall within the scope of claim 22.

The subject-matter of claims 12, 13 and 19-22 is therefore novel (Article 33(2) PCT).

3. Inventive Step

3.1 Concerning independent claim 1, document D2 is considered to represent the most relevant state of the art.

The problem to be solved by the present invention may therefore be regarded as provision of alternative compounds suitable for use in the treatment of immune diseases or cancer.

The solution proposed in claim 1 of the present application can be considered as involving an inventive step (Article 33(3) PCT), because there is no teaching in the prior art that would have lead the skilled person to the compounds according to claim 1 and their pharmaceutical activity could not be expected.

Accordingly, claims 12, 13 and 19-22 pertaining to the use and preparation of

these compounds can also be considered as involving an inventive step (Article 33(3) PCT).

3.2 Dependent claims 16 and 18 pertain to obvious selections and do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.